Osteosarcopenia: Where Osteoporosis and Sarcopenia Collide

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Abstract

The coexistence of osteoporosis and sarcopenia has been recently considered in some groups as a syndrome termed ‘osteosarcopenia’. Osteoporosis describes low bone mass and deterioration of the micro-architecture of the bone, whereas sarcopenia is the loss of muscle mass, strength and function. With an ageing population the prevalence of both conditions is likely to increase substantially over the coming decades and is associated with significant personal and societal burden. The sequelae for an individual suffering from both conditions together include a greater risk of falls, fractures, institutionalisation and mortality. The aetiology of ‘osteosarcopenia’ is multifactorial with several factors linking muscle and bone function including genetics, age, inflammation and obesity. Several biochemical pathways have been identified which are facilitating the development of several promising therapeutic agents which target both muscle and bone. In the current review we outline the epidemiology, pathogenesis and clinical consequences of ‘osteosarcopenia’ and explore current and potential future management strategies.

Key words

Bone, muscle, osteoporosis, sarcopenia, osteosarcopenia, falls, fracture, strength.

Introduction

Osteoporosis and sarcopenia are both common age-associated diseases which often co-exist. Within an ageing population the prevalence of both these conditions is expected to rise in the future, increasing the risk of fragility fractures, which are themselves associated with significant morbidity and mortality [1]. Hence, losses in independence seen in later life are associated with both bone and muscle loss [2].

The economic burden of osteoporotic fragility fractures is high, costing approximate £4 billion per annum in the UK [3]. Osteoporosis is characterized by deterioration in bone microarchitecture resulting in reduced bone mineral density (BMD), increased bone fragility and a heightened risk of fracture even as a consequence of minor trauma [4]. [5].

Unlike osteoporosis, the economic burden of sarcopenia is poorly characterized, although one study estimated direct costs attributable to sarcopenia in the USA, in the year 2000, to be $18.5 billion [6]. A recent systematic review exploring the healthcare costs of sarcopenia showed a large heterogeneity between studies but, globally, showed trends towards greater healthcare costs for the sarcopenic population [7]. The etymology of sarcopenia is from the Greek ‘sarx’ for muscle and ‘penia’ meaning ‘loss’ [8]. It is a condition characterized by progressive, age-related loss of muscle mass and function. Unlike osteoporosis, no single broadly accepted clinical definition of sarcopenia has yet been established, although all definitions recognise that measuring muscle mass in isolation is inadequate, as a measure of muscle function is also required. Sarcopenia was previously defined, in 2010, by the European Working Group on Sarcopenia (EWGSOP) as the presence of low muscle mass, reduced muscle strength and physical performance [9]. This definition was updated in 2019 (EWGSOP2) with a greater focus on low muscle strength as the primary parameter characterising sarcopenia [10]. The new definition defines sarcopenia as reduced hand grip strength or chair stand test together with a

reduced skeletal muscle mass index, with severe sarcopenia defined as additional poor physical performance, as assessed by gait speed, timed up and go, short performance battery test and 400 metre walk test. A further definition of sarcopenia proposed by the Foundation for the National Institutes of Health (FNIH) Sarcopenia Project, similarly comprises grip strength and ALM/BMI (ratio of appendicular lean mass over body mass index [BMI]) [9]. Epidemiological studies have found an association between sarcopenia and falls history, whether defined by the EWGSOP [11,12] or by using ALM/BMI [13]. Furthermore, a study of older community-dwelling individuals from the Hertfordshire Cohort Study (HCS) has shown that sarcopenia, as defined using the FNIH definition, is associated with higher prevalent fractures [14].

When osteoporosis and sarcopenia occur in consort it has recently been suggested that they are referred to as 'osteosarcopenia' [7. It should be noted that the few studies that have considered this issue suggest the risks of serious morbidity are notably higher when osteoporosis and sarcopenia co-exist [15]. Furthermore, evidence showing overlap in the pathophysiology of sarcopenia and osteoporosis raises the possibility of common potential treatments for the two conditions [16]. Indeed, new medications are being developed which exploit the cross-talk between bone and muscle and will be explored in this review [17].

Prevalence of coexistence of osteoporosis and sarcopenia

Bone mass typically reduces by approximately 30% between the third and seventh decades [18] and it is estimated that 1 in 3 women and 1 in 5 men over the age of 50 years will suffer a fragility fracture [19]. In older people, fractures occur more frequently in females, with rates becoming approximately twice those of men over the age of 50; in older individuals, the forearm, hip and vertebrae are the sites most susceptible to fracture [20].

Muscle fibre parameters appear relatively stable until the end of the fourth decade of life, after which muscle fibre loss accelerates resulting in approximately 30% loss of muscle mass by 80 years of age [9]. Sarcopenia is a common condition of ageing with a prevalence in community-dwelling older individuals varying from between 1 and 29% in populations over the age of 50 years, based on the EWGSOP [21] and is projected to affect more than 200 million individuals worldwide in the next 40 years [9].

In contrast to osteoporosis and sarcopenia considered individually, there are few data on the epidemiology of osteosarcopenia, as the condition has only recently been proposed. A UK study has reported that in osteoporotic postmenopausal females the prevalence of sarcopenia was 50% [15], while a study by Di Monaco and colleagues of 340 Italian Caucasian women with hip fracture, who subsequently underwent DXA scanning, showed that for sarcopenic woman the adjusted OR for T-Score ≤-2.5 was 1.80 (95%CI 1.07–3.02) [22]. Evidence supports an increased prevalence of osteosarcopenia with advancing age, with a Chinese study of adults over the age of 80 years reporting rates of 10.4% in men and 15.1% in women [23]. More recently, a study of 288 older subjects in Belgian showed that sarcopenic subjects had a 4-fold higher risk of having co-existing osteoporosis compared with non-sarcopenic individuals (OR = 4.18; 95% CI 1.92–9.12) [24].

Consequences of the coexistence of osteoporosis and sarcopenia in patients

Coexistence of sarcopenia and osteoporosis has been associated cross-sectionally with depression, malnutrition, peptic ulcer disease, inflammatory arthritis and reduced mobility [15]. Studies from Australia and China have demonstrated that individuals with both osteoporosis and sarcopenia are at higher risk of falls and fractures than those with osteoporosis

or sarcopenia alone [15,23]. The resultant fractures, and particularly hip fractures, are associated with significant morbidity; approximately half of previously ambulatory individuals are unable to mobilise independently post hip fracture [25]. Furthermore, 55% of individuals above 90 years of age are unable to live independently following fracture [25]. Frailty is defined as a multidimensional syndrome of loss of reserves (energy, physical ability, cognition, health) that gives rise to vulnerability in older people [26]. A number of older people are both frail or prefrail, and also have osteoporosis and sarcopenia; in one study the conditions were found to co-exist in 26.3% of frail men and 38.5% of frail women (compared to 1.6% of non-frail men and 1.9% of non-frail women) [23]. In a study of Korean hip fracture patients, where 1 year mortality overall was remarkably low, the presence of osteosarcopenia was associated with a 1-year mortality rate of 15.1% compared to patients with osteoporosis (5.1%) or sarcopenia alone (10.3%) [27].

Factors associated with osteoporosis and sarcopenia

Genetic factors

Genetic factors are important in the achievement of peak bone mass [28]. [29]. Recent data from UK Biobank suggest that muscle strength, and therefore likely sarcopenia, is also partially genetically regulated [30]. Vitamin D receptor polymorphisms have been shown to be associated with both sarcopenia and osteoporosis [31].

Alcohol

Excess alcohol intake has a detrimental effect on skeletal health. In addition to its direct toxic effect on osteoblast function, there are additional adverse effects on gonadal function, protein metabolism, calcium metabolism, physical activity and falls risk [32-34]. A meta-analysis

conducted by Kanis and colleagues showed that drinking above 2 units of alcohol a day is associated with an increased risk of fracture [35]. There is limited evidence linking alcohol use to muscle mass but a study of 608 community-dwelling older men in France has demonstrated that heavy alcohol intake (>210 g/week) is associated with low muscle mass [36].

Cigarette Smoking

Like alcohol, cigarette smoking has a deleterious effect on both bone and muscle health. A meta-analysis by Law and colleagues demonstrated worse bone health in female smokers compared with non-smokers[37]. The mechanism through which cigarette smoking impacts upon BMD and fracture risk is multifactorial and likely to include the increased likelihood of early menopause, on average 9 months earlier, enhanced metabolism of exogenous oestrogens and reduced body weight [2]. Both smoking and alcohol intake are well established risk factors for fracture and are therefore included in the FRAX^{TM} fracture risk assessment tool [38].

There is less evidence linking cigarette smoking to loss of muscle mass but a recent meta-analysis showed cigarette smoking was associated with an increased risk of developing sarcopenia [39]. The association between cigarette smoking and sarcopenia may be as a consequence of smoking being associated with low levels of physical activity and low BMI [40,41].

Physical activity

Physical activity levels have a profound impact on both bone and muscle health. Studies have demonstrated that physical activity prevents bone loss; the most effective type of exercise intervention on femoral neck BMD appears to be non-weight bearing high force exercise such as progressive resistance strength training for the lower limbs while the most effective intervention for spine BMD was combination exercise programmes[42]. Conversely,

prolonged immobilisation is associated with reduction in BMD and increased fracture risk [43]. There are several trials which have shown that exercise in older people results in improved muscle mass and physical performance [44]. [45].

Diet

There is evidence to suggest that a good diet is essential for the development and maintenance of good bone and muscle health. For example, adequate calcium and vitamin D intake has been linked to both bone and muscle mass [46]. Weak evidence was detected to support a reduction in fracture risk when taking calcium alone [RR 0.90 (95% CI 0.80, 1.00)]. By contrast, a meta-analysis conducted by Bischoff-Ferrari and colleagues found a potentially increased risk of hip fracture in individuals taking calcium supplementation alone, although a relatively low number of participants were included [47]. The analysis performed by Tang and colleagues showed that when calcium and vitamin D supplementation were combined, the RR of any fracture was 0.87 (95% CI 0.77, 0.97), compared with 0.90 (95% CI 0.80, 1.00) for calcium alone [46]. Additionally, a meta-analysis conducted by Bolland and colleagues demonstrated that a combination of calcium with vitamin D supplementation reduced the risk of all fractures (RR 0.89 (95% CI 0.86, 0.99)) and vertebral fractures (RR 0.86 (95% CI 0.74, 1.00)), but not forearm or hip fractures [48]. Overall, these data suggest that a combination of vitamin D and calcium supplementation affords a modest reduction in fracture risk and is more effective than calcium supplementation alone. There is less evidence for the use of calcium supplementation alone in reducing muscle mass and function decline [49,50]. There is evidence to suggest that supplementation with vitamin D has a small yet significant effect on increasing muscle strength, but not muscle mass or power [51]. The effect was most pronounced in patients with baseline vitamin D deficiency. Furthermore, experimental studies have demonstrated both histological and electrophysiological changes in muscle in severe vitamin D deficiency [52-54]. There is some evidence to suggest that dietary protein intake may also be important for

maintaining bone and muscle mass [55]. For example, it has been demonstrated in participants from the Shanghai Women's health Study that that a high soy consumption is associated with a lower risk of fracture [56] and that in fasting older subjects, muscle protein synthesis is reduced [57].

Age, sex and ethnicity

Advancing age and female sex is associated with the development of both osteoporosis and sarcopenia. It has been estimated that in American women over the age of 85, 70% are osteoporotic at the hip, lumbar spine or forearm and a further 27% are osteopenic, whereas the majority of women under the age of 50 years have normal BMD [58]. Epidemiological studies have shown that in Caucasian women aged 50 years, the remaining lifetime risk of fragility fracture is 17.5% for hip fracture, 15.6% for vertebral fracture and 16% for distal forearm fracture. The corresponding risk for men is 6%, 5% and 2.5% [19]. It has been estimated that the prevalence of sarcopenia is 5-13% for adults aged 60-70 years and increases to 11-50% for adults aged above 80 years [59]. North American studies have shown that age- and sex-adjusted hip fracture rates are generally higher in White than in Black or Asian populations [60] and higher muscle mass has been described in Black populations [61].

Osteosarcopenic obesity

Low BMI is a risk factor for low BMD and for fragility fracture, with individuals with a BMI $<20 kg/m^2$ at the greatest risk [2]. Conversely, studies have suggested that obesity can be a protective factor against bone loss [62-64]. Interestingly, obesity is not protective against fracture at all skeletal sites with an increased fracture risk at the proximal humerus, upper leg, and ankle [65,66]. Furthermore, low-trauma fractures are equally prevalent in obese and non-

obese women [66]. The protective effect of adiposity on bone mass at some skeletal sites may be in part explained by the well documented relationship between peripheral oestrogen levels and obesity, with most circulating oestrogens produced in fat tissue via conversion of androgens post menopause [62]. Obese individuals have a greater absolute maximum muscle strength compared to non-obese persons, suggesting that increased adiposity acts as a chronic overload stimulus on muscles and so increasing muscle size and strength. However, when maximum muscular strength is normalised to body mass, obese individuals appear weaker. [67] which leads to an impairment of physical function [44,45]. With advancing age the composition of body tissue changes with an overall increase in body fat and decrease in muscle mass, which often occurs despite overall body weight remaining stable. This excess adipose tissue in combination with low muscle mass has been termed 'sarcopenic obesity' and has been shown to be associated with impaired function and increased disability [68,69].

Pathophysiology

Muscle and bone function are closely related with shared mechanical and molecular mechanisms. The mechanical interaction between muscle and bone is described by the 'mechanostat' theory, which states that muscle imposes mechanical forces on bone, and if these exceed a set threshold the equilibrium of bone turnover shifts away from bone resorption in favour of bone formation [70]. It is thought that this occurs as increases in muscle mass induce the stretching of periosteum and collagen fibres which results in the stimulation of bone growth [71]. As both bone and muscle mass are intrinsically linked to the reduction in physical performance observed with ageing this lends credence to the importance of mechanical loading in the maintenance of the bone-muscle unit.

The molecular mechanisms linking bone to muscle function, known as bone-muscle cross-talk, are less well defined. Hormones identified as playing a key role in the development of osteosarcopenia include growth hormone/insulin-like growth factor-1 (GH/IGF1) and gonadal sex hormones [17]. Human muscle and bone cells both express oestrogen receptors, hence hormone replacement therapy in post-menopausal women is able to both preserved bone and muscle mass [72]. Furthermore, early menopause without treatment with exogenous oestrogen is a strong risk factor for future fragility fracture [73]. The pathogenesis of male age-related osteoporosis and sarcopenia are less well characterised but it is thought that oestrogens derived from the metabolism of androgens play a role in preserving bone mass and that low testosterone results in reduced protein synthesis with the subsequent loss of muscle mass [74]. Indeed, low testosterone levels in older men are predictive of frailty and incident falls [75,76]. GH and IGF1 both exert a positive influence on osteoblasts in addition to their anabolic actions on muscle [77].

Chronic non-communicable diseases such as chronic obstructive pulmonary disease (COPD), heart failure and malignancy are associated with cachexia which describes the loss of body weight including lean muscle mass. Cachexia is associated with the increased production of pro-inflammatory cytokines (particularly IL-6, Il-1 and TNF) and the resultant inflammatory state results in loss of bone and muscle mass. ‘Inflammaging’ describes a mechanism through which bone and muscle mass are likely linked. The term inflammaging was originally coined in the year 2000 to describe chronic, low grade inflammation that increases with age and is a significant risk factor for morbidity and mortality in older people [78]. This increase in the levels of background inflammation with age is thought to occur as a result of cumulative exposure to environmental and infective antigens which result in the production of reactive oxygen species (ROS). ROS stimulate the release of additional cytokines from the innate and acquired immune system, thus tipping the immune balance in favour of a chronic inflammatory

state [79]. Studies have linked chronically raised inflammatory cytokines to the development of sarcopenia, possibly through the activation of the ubiquitine-protease pathway [80,2] and increased pro-inflammatory cytokines such as TNF-α, IL-1 and IL-6, which promote bone resorption [81,82]. Furthermore, epidemiological studies have shown positive associations between both osteoporosis and sarcopenia and C-reactive protein (CRP) which is a marker of active inflammation [83-89].

Factors known as myokines, released from muscle, and osteokines, released from bone such as osteocalcin are known to be one mechanism of communication between the two tissues. A myokine called myostatin has been extensively studied and has been shown in mice to play an important role in the impaired proliferative capacity of muscle and bone progenitor cells with ageing [90]. Furthermore, the Wnt-β-catenin signalling pathway has been shown to mediate bone-muscle crosstalk by controlling both osteoblastic activity and muscle regeneration [91]. Understanding the molecular pathways by which muscle and bone interact provides potentially exciting molecular targets for the development of therapeutics for the treatment of osteosarcopenia.

Management of osteosarcopenia

Both osteoporosis and sarcopenia are amenable to therapeutic interventions, although many more pharmaceutical agents are currently available for the treatment of osteoporosis. Lifestyle interventions include ensuring adequate protein intake, progressive resistance exercise and vitamin D replacement when necessary.

Physical activity and exercise

As previously discussed, physical activity has a profound effect on both bone and muscle strength. Prolonged immobilisation is a well-established risk factor for loss of bone density [2] and a meta-analysis has demonstrated that physical activity has a significant protective effect on BMD at the lumbar spine [42]. Furthermore, a meta-analysis of 14 prospective studies has shown a significant inverse relationship between increasing level of physical activity and risk of hip fracture in older women [92]. Similarly studies have shown that lifelong physical exercise serves to preserve muscle structure and function [93] and increases in mid-life physical activity reduces the risk of impaired mobility in later life [94,95]. There is evidence to suggest that resistance training is the most effective form of physical exercise to improve muscle strength and physical performance in older people [96].

Nutrition

Adequate vitamin D intake is associated with better BMD and muscle mass and function; a linear positive association was observed between BMD and serum 25(OH)D level up to a level of 75nmol/l in white US populations [97]. Indeed, to prevent age-related deterioration in musculoskeletal health the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) recommends a vitamin D intake of 800IU/daily to maintain 25(OH)D levels >50 nmol/l in post-menopausal women [2]. Adequate protein intake is essential, with 5-12% of older men and 20-24% of older women consuming inadequate levels (<0.66g/kg body weight per day) in the USA [98]. To increase the anabolic response to protein in older people, it has been suggested that a higher protein intake of 1.0-1.2g/kg body weight per day is taken post exercise [99]. A recent meta-analysis to explore whether the use of nutritional supplementations improves physical performance in older people showed nutritional supplementation can improve a number of physical performance outcomes, particularly when they include multi-nutrients and in people already affected by specific medical conditions, or by frailty/sarcopenia [100].

Therapeutic targets

As pharmacotherapy for osteoporosis is well established, the majority of medications currently used in the management of osteosarcopenia are focused on targeting bone separately from muscle, and include bisphosophonates, denosumab and teriparatide therapy. As osteoporosis and sarcopenia are associated, several new therapies are currently being developed to target bone and muscle in tandem. For example, selective androgen receptor modulators (SARMs), such as andarine, have an anabolic effect on muscle and bone, with few of the androgenic side effects associated with testosterone therapy [17]. Another potential therapeutic target is irisin, a hormone-like myokine produced in abundance by skeletal muscle cells in response to exercise. Following its release into the circulation, irisin acts upon white adipocytes inducing the browning response and subsequently activating non-shivering thermogenesis [101]. Promisingly, recent studies have also suggested a role for irisin on the musculoskeletal system with positive effects on cortical mineral density and geometry in mice with upregulation of the irisin precursor (FNDC5) in skeletal muscle fibres [102]. Myostatin is a myokine associated with impaired muscle and bone mass with ageing and the myostatin inhibitor 'follistatin' has been shown to induce significant improvement in diabetic bone regeneration in mice [103]. As detailed previously, osteosarcopenia may, at least in part, be a lipotoxic disease and *in vitro* studies have demonstrated that inhibiting fatty acid synthetase using cerulenin, which prevents adipose cells from releasing fatty acids, rescues osteoblasts from fat-induced toxicity and cell death [104]. Furthermore, treatment *in vivo* with cerulenin has been shown to protect osteoblasts from lipotoxicity while rescuing oophorectomized mice from their osteoporotic phenotype [105]. Other potential therapeutic targets which are currently being explored include anti-sclerostin antibodies, cathepsin K inhibitors and GH secretagogues.

Conclusion

The coexistence of osteoporosis and sarcopenia is an increasingly recognised condition which is associated with significant morbidity, mortality and societal cost. As the population ages, its prevalence is set to increase dramatically over the coming decades with an estimated 2 billion individuals over 60 years of age affected by the year 2050 [9]. Identifying those individuals at risk of developing coexisting osteoporosis and sarcopenia, may enable clinicians to intervene and ameliorate the consequences of osteosarcopenia.

Key messages

1. Osteosarcopenia is a newly proposed syndrome which describes the coexistence of osteoporosis and sarcopenia
2. Sequelae of osteosarcopenia include increased risk of falls and fractures, leading to significant public health burdens
3. Novel pharmacological agent that might target both bone and muscle have been proposed and are under evaluation

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